Received: 19 November 2019 | Revised: 30 April 2020 | Accepted: 4 May 2020

DOI: 10.1111/myc.13100

ORIGINAL ARTICLE

mycoses Diagnosis, Therapy and Prophylaxis of Fungal Diseases WILEY

Intravenous itraconazole compared with liposomal amphotericin B as empirical antifungal therapy in patients with neutropaenia and persistent fever

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Summary

Background: Fungal infections are a major complication of neutropaenia following chemotherapy. Their early diagnosis is difficult, and empirical antifungal treatment is widely used, and uses of less toxic drugs that reduce breakthrough infection are required.

Objective: We conducted a multicentre, open-label, randomised, non-inferiority trial to compare the safety and efficacy of intravenous itraconazole (ivITCZ) and liposomal amphotericin B (LAmB) as empirical antifungal therapy in patients with haematological malignancies with neutropaenia and persistent fever.

Methods: Patients with haematological malignancies who developed fever refractory to broad-spectrum antibacterial agents under neutropaenia conditions were enrolled. Patients were randomised for treatment with LAmB (3.0 mg/kg/d) or ivITCZ (induction: 400 mg/d, maintenance: 200 mg/d).

Results: Observed overall favourable response rates of 17/52 (32.7%) and 18/50 (36.0%) in the LAmB and ivITCZ groups, with a model-based estimate of a 4% difference (90% CI, −12% to 20%), did not fulfil the statistical non-inferiority criterion. In the LAmB group, there were two cases of breakthrough infection and five cases of probable invasive fungal disease, whereas in the itraconazole group, neither breakthrough infection nor probable invasive fungal disease occurred. Patients in the

Clinical Trial Registration: UMIN-CTR identifier: UMIN000005529

https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000006558

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Funding information
Grant-in-Aid for Clinical Research from the National Hospital Organization

ivITCZ group had significantly fewer grade 3-4 hypokalaemia-related events than LAmB group patients ($P < .01$). The overall incidence of adverse events tended to be lower in the ivITCZ group ($P = .07$).

Conclusion: ivITCZ showed similar efficacy and safety as LAmB as empirical antifungal therapy in haematological malignancy patients with febrile neutropaenia, although the small sample size and various limitations prevented demonstration of its non-inferiority.

KEYWORDS
antifungal agents, chemotherapy-induced febrile neutropaenia, haematological malignancies, hypokalaemia, intravenous itraconazole, liposomal amphotericin B, probable invasive fungal disease, prospective randomised controlled trial

1 | INTRODUCTION

Febrile neutropaenia, one of the most serious complications that occur following chemotherapy for haematological malignancies, is caused by bacterial or fungal infections.[1-3]

Given the resistance or breakthrough infections seen with fungi that are resistant to already existing antifungal agents,[4-8] it is increasingly important to select the right antifungal agent for applications such as prophylaxis, empirical treatment and pre-emptive treatment.

A previous prospective study compared empirical treatment of liposomal amphotericin B (LAmB) with amphotericin B deoxycholate as the control group.[9] The results showed that LAmB was equally effective as amphotericin B deoxycholate and more safety. Subsequently, prospective comparative studies between LAmB and voriconazole,[10] and LAmB and caspofungin[11] were performed, which showed that voriconazole was inferior and caspofungin was non-inferior to LAmB. Therefore, caspofungin is currently considered the standard of care as empirical therapy. However, there are many reports of breakthrough fungal infections after treatment with echinocandin-type antifungal agents, such as caspofungin.[4,8,12]

Itraconazole (ITCZ) is a triazole antifungal agent with broad-spectrum activity against *Candida*, *Aspergillus*, *Trichosporon* and mucormycosis. However, the originally developed ŀTCZ capsule has poor intestinal absorption and the concentrations are not stable but have a high intra- and interindividual variability. To overcome this weakness, intravenous itraconazole (ivITCZ) was developed. The results of a prospective, randomised study comparing ivITCZ and the conventionally used intravenous amphotericin B deoxycholate[13] concluded that ivITCZ showed similar efficacy and increased safety as empirical fungal therapy.

ivITCZ has a broad antifungal spectrum in vitro, including against *Aspergillus* species, [14] and good bioavailability. We hypothesised that ivITCZ, which is non-inferior to amphotericin B deoxycholate, would have similar efficacy and lower toxicity as compared to LAmB as a control drug. Therefore, we planned a prospective randomised, non-inferiority study of ivITCZ and LAmB.

2 | PATIENTS AND METHODS

This multicentre study was approved by the institutional review board of each participating institution. All patients provided written informed consent prior to enrolment. The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to and the appropriate ethical review committee approval has been received.

Patients aged 20-79 years who received chemotherapy for haematological malignancies were eligible for this study within 30 days. Neutrophil count was less than 500/μL for at least 96 hours in all the

patients. Patients who had a fever with an axillary body temperature of more than 37.4°C persisting more than 96 hours after the start of treatment with broad-spectrum antibacterial drugs were enrolled. Patients with proven invasive fungal disease or confirmed bacterial or viral infection at enrolment, along with a history of fungal infection, were excluded. A prospective randomised controlled trial was conducted with five stratification factors (risk, antifungal prophylaxis, age ≥ 60 years, gender and institution). High-risk patients were defined as those after allogeneic transplantation or chemotherapy for recurrent acute leukaemia; low risk was defined as otherwise. Only prophylactic administration of amphotericin B syrup, micafungin and miconazole gel was allowed. Registration of such patients was possible if the previous prophylactic antifungal agent was terminated 2 weeks before study enrolment. Details of this are described elsewhere.[15]

In the LAmB group, 3.0 mg/kg body weight of LAmB was administered intravenously. If significant weight gain (±10%) occurred for reasons other than fluid retention, the dose was adjusted. In the ivITCZ group, 200 mg of itraconazole was administered as an intravenous infusion. The first five doses were administered at 12-hour intervals, while they were administered at 24-hour intervals from the sixth dose onwards.

In all patients, chest computed tomography (CT), blood culture tests and β-D-glucan and galactomannan antigen assays were performed before and after the start of study treatment, and plasma levels of β-D-glucan and galactomannan antigen assays were performed weekly and chest CT were performed biweekly thereafter. Blood culture tests were also performed at the end of the study treatment. Based on these results, fungal infection was evaluated using the 2008 updated European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) consensus group efficacy criteria.[16]

The primary endpoint of this study was the presence or absence of an overall favourable response (OFR). Patients meeting all five of the following criteria were considered to have an overall favourable response. Additionally, cases meeting criteria (2) through (4) in the absence of any baseline infection were also considered to have an overall favourable response.

1. Successful treatment of baseline infection by the end of the study treatment;
2. Absence of breakthrough infection;
3. Survival until 7 days after completion of treatment;
4. No discontinuation of treatment due to drug-related toxicity; and
5. Resolution of fever during neutropaenia (axillary temperature ≤ 37.4°C for at least 48 hours).

The secondary endpoints were as follows:

1. Successful treatment of baseline infection
2. Development of breakthrough infection
3. Survival until 7 days after completion of treatment
4. Discontinuation of treatment due to drug-related toxicity
5. Resolution of fever during neutropaenia
6. Adverse events (AEs)

AEs occurring from the start of treatment until 14 days after the end of treatment were assessed for category and worst grade according to Common Terminology Criteria for Adverse Events (CTCAE) ver. 3.0.

7. Probable invasive fungal disease.[16]

2.1 | Statistical analysis

This study intended to demonstrate the principal hypothesis that ivITCZ is not more than 10% inferior (acceptable range) in terms of OFR compared to treatment with standard LAmB therapy. The sample size needed to demonstrate non-inferiority with a 5% one-sided significance level and 90% power was calculated as 395 subjects per group, and a target sample size of 850 subjects was deemed essential in consideration of ineligible cases. Associations between the primary and secondary endpoints and treatment interventions were assessed using Fisher's exact test for superiority. All other statistical tests were two-sided and interpreted at the 5% significance level.

Upon enrolment, patients were randomly assigned to either group using an electronic data capture and allocation system. The random allocation factors included risk (high or low), prophylactic antifungal treatment (yes or no), study institution, sex and age (age at enrolment <60 years or ≥60 years). High-risk subjects were defined as allograft patients or patients with recurrent acute leukaemia. All other patients were considered low risk. An academic statistician conducted all analyses using SAS software version 9.4 (SAS Institute).

3 | RESULTS

One hundred and three patients with a median age of 60 years (range 51-68 years) were enrolled from 12 centres of the National Hospital Organisation in Japan between March 2011 and February 2015 and randomly assigned to two groups, the LAmB group (53 patients) and the ivITCZ group (50 patients), for the intention-to-treat (ITT) analysis (Figure 1). Two of the 53 patients assigned to the LAmB group and one of the 50 assigned to the ivITCZ group discontinued the study due to deviations from the enrolment criteria. Of the two LAmB group patients who were found ineligible, the fever in one of them was of less than 96 hours duration under neutropaenic conditions, while the other patient was found to have blood cultures proven of *Candida glabrata* at enrolment. The excluded patient in the ivITCZ group showed coagulase-negative staphylococci on blood culture testing that was performed at the time of study enrolment. Therefore, these patients were disqualified before treatment began and were excluded from the study.

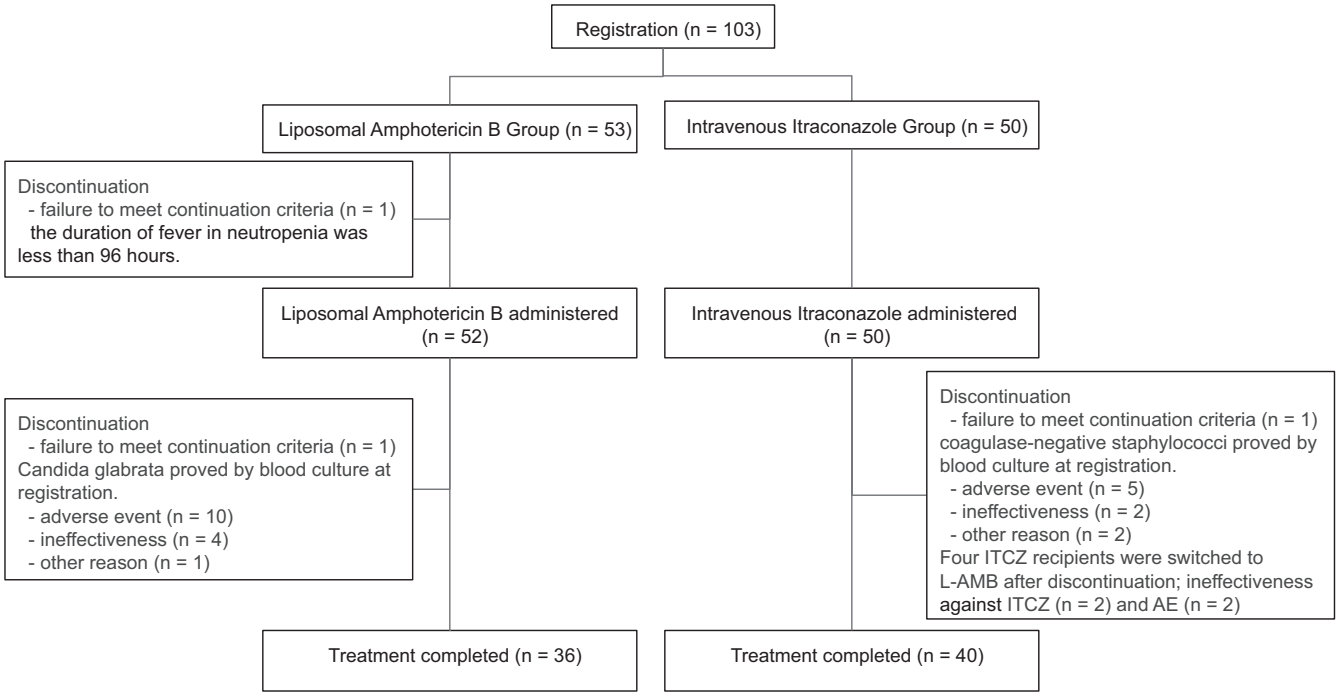

FIGURE 1 Diagram of participant enrolment

Approximately half of all patients were male, over the age of 60 years. About one-third of all patients were at high risk and were receiving antifungal prophylaxis. The two groups were similar in terms of age at enrolment, gender, risk, prophylactic antifungal treatment and disease extent (Table 1).

Ten patients discontinued treatment due to toxicity of LAmB and five patients discontinued treatment due to toxicity of ivITCZ. The difference between the groups was not statistically significant (19.2% vs 10.0%; $P = .26$). The study treatment completion rate in the LAmB group was 69.2% (95% CI 54.9%-81.3%), and that in the ivITCZ group was 80.0% (95% CI 66.3%-90.0%) ($P = .26$).

The main reason for discontinuing study treatment was the toxicity associated with each group's study intervention. Four patients in the ivITCZ group who discontinued study treatment switched to LAmB as alternative systemic antifungal therapy within 7 days of discontinuation. None of the patients in the LAmB group switched to ivITCZ.

The average number of days of study treatment in the LAmB group was 14.4 days (range 1-47 days), and the first actual dose administered in this group was 162.6 ± 24.2 mg per dose. The average number of days of study treatment in the ivITCZ group was 14.0 days (range 5-32 days), with a single dose of 200 mg per dose, with 30% of patients receiving two doses on the first day of treatment.

The OFR rate was 32.7% in the LAmB group and 36.0% in the ivITCZ group, with a difference of 4% (90% CI, −12% to 20%), which did not meet the statistical criteria for itraconazole non-inferiority (Table 2). These rates were not related to antifungal prophylaxis or risk. All patients in both groups survived until 7 days after termination of the antifungal treatment. Results were no statistical significance between the two groups for documented breakthrough fungal infections (LAmB vs itraconazole, 3.8% vs 0.0%, $P = .50$), treatment discontinuation due to drug-related toxicity (LAmB vs itraconazole, 19.2% vs 10.0%, $P = .26$) and fever resolution during neutropaenia (LAmB vs itraconazole; 38.5% vs 42.0%, $P = .84$). There were no baseline fungal infections in either group. Breakthrough infections were observed only in the LAMB group. Of two patients diagnosed with a breakthrough infection, *Candida albicans* was detected in a blood culture test in one patient and a Candida species was detected in a liver biopsy specimen in the other patient. The former case was probably a result of progression from invasive fungal disease. Five patients who received LAmB were subsequently diagnosed with a probable invasive fungal disease, but none of the patients who received ivITCZ had probable invasive fungal disease ($P = .06$). Of the five patients diagnosed with probable invasive fungal disease in the LAmB group, CT imaging findings were compatible with fungal infection in all five patients. In both β-D-glucan and galactomannan antigen tests, two subjects had higher cut-off values. CT before the start of the study was performed in 45 cases. There were 39 cases of chest CT, 2 cases of abdominal CT and 2 cases of whole-body CT. Follow-up CT was performed in 32 cases. There were 29 cases of chest CT, 1 case of abdominal CT and 2 cases of whole-body CT. The follow-up CT in this study remained at about 30%.

AEs that occurred between the start of study treatment and 14 days after the end of treatment included hypokalaemia, γ-glutamyl transferase elevation, alanine transaminase elevation and nausea in the LAmB group, and hypokalaemia, dyspnoea and hypoxaemia in the ivITCZ group (Table 3). The cumulative number of grade 3-4 AEs in the LAmB and ivITCZ groups was 297 and 248,

TABLE 1 Patient characteristics

Characteristic		Liposomal Amphotericin B (N = 52)	Intravenous Itraconazole (N = 50)	Total
Age at enrolment (y)	<60	25	22	47
	≥60	27	28	55
Sex	Male	27	27	54
	Female	25	23	48
Risk	High[a]	13	15	28
	Low	39	35	74
Prophylactic antifungal treatment	Yes[b]	18	14	32
	No	34	36	70
Disease	Acute myelogenous leukaemia	35	33	68
	Acute lymphoblastic leukaemia	2	3	5
	Mixed phenotype acute leukaemia	0	1	1
	B-cell non-Hodgkin lymphoma, multiple myeloma	9	9	18
	Natural killer cell/T-cell lymphoma	1	2	3
	Hodgkin lymphoma	2	0	2
	Myelodysplastic syndrome/ Myeloproliferative neoplasm	0	1	1
	Myeloproliferative neoplasm	3	0	3
	Myelodysplastic syndrome	0	1	1

[a]High-risk patients were defined as patients after allogeneic transplantation or chemotherapy for recurrent acute leukaemia; low risk was defined as otherwise.

[b]Only amphotericin B syrup, micafungin and miconazole gel were allowed as prophylactic drugs. For patients who received any of these drugs, registration for participation in this study was allowed if the previous antifungal agent was terminated 2 weeks before the start of study enrolment.

respectively. The frequency of these events tended to be higher in the LAmB group than in the ivITCZ group ($P = .07$). The ivITCZ group had five cases of grade 3 dyspnoea and six cases of grade 3 hypoxia. The corresponding number of cases in the LAmB group was two each. The incidence of grade 3 and 4 hypokalaemia was 18 (34.6%) and 11 (21.2%) in the LAmB group and 9 (18.0%) and 5 (10.0%) in the ivITCZ group, respectively. The ivITCZ group had a significantly lower incidence of grades 3-4 hypokalaemia compared to the LAmB group ($P < .01$).

4 | DISCUSSION

This is the first randomised controlled trial to directly compare LAmB with ivITCZ as empirical antifungal therapy in patients with persistent febrile neutropaenia, although the number of cases assessed was much smaller than what was originally planned. After study commencement, the number of participants did not increase due to factors such as the approval of caspofungin for use in Japan after the start of the study and the limited number of prophylactic antifungal drugs allowed in the protocol. The reason for limiting prophylaxis was due to the fact that itraconazole is an azole antifungal and that fluconazole, which is often used as a prophylactic, is also an azole antifungal. In the protocol at the start of the study, if another antifungal drug was used, registration in the study was only allowed after more than 4 weeks had elapsed since discontinuation of the previous drug, although the protocol was revised to allow patient registration if more than 2 weeks had elapsed from discontinuation of previous antifungal therapy. Nevertheless, the number of cases registered still did not increase adequately. Prior to the start of this study, an interim analysis was planned, with a final analysis with a 4.9% significance level and an interim analysis with a 0.1% significance level. Since the interim analysis was not actually performed, the analysis was performed at a significance level of 5% (corresponding to the 90% CI). At this level of significance, the OFR ratio was 32.7% in the LAmB group and 36.0% in the ivITCZ group, indicating slightly better results in the ivITCZ group (difference in the ratio of 0.04). However, for the determination of non-inferiority, the lower limit of the 90% CI was −0.12, which was smaller than the preset tolerance (non-inferiority margin) of −0.10. Hence, the non-inferiority of ivITCZ was not proved. Successful treatment of baseline infection and resolution of fever during neutropaenia as a component of OFR may have been limiting. The definition of axillary temperature ≤37.4°C for at least 48 hours is too strict that makes it difficult to compare with other studies.

The overall safety profile tended to be better in the ivITCZ group than in the LAmB group ($P = .07$). The difference was especially noticeable for hypokalaemia ($P < .01$). Four patients in the ivITCZ group who discontinued study treatment switched to LAmB within 7 days of discontinuation. The reasons for discontinuation were

TABLE 2 Clinical outcomes

Variables	Liposomal Amphotericin B(N = 52)		Intravenous Itraconazole (N = 50)		Difference in proportions[a]	90% CI		95% CI		*P*-value
	N	%	N	%						
Overall favourable response	17	32.7	18	36.0	0.04	−0.12	0.20	−0.15	0.23	-
Successful treatment of baseline infection by the end of treatment[b]	-		-		-	-	-	-	-	-
Absence of breakthrough infection	50	96.2	50	100.0	0.04	-	-	−0.27	0.34	.50
Survival 7 d after termination of antifungal treatment[c]	52	100.0	50	100.0	0	-	-	-	-	1.00
No discontinuation of antifungal treatment due to drug-related toxicity	42	81.8	45	90.0	0.11	-	-	−0.08	0.30	.26
Fever resolution during neutropenia (axillary temperature ≤ 37.4°C for at least 48 h)	20	38.5	21	42.0	0.04	-	-	−0.15	0.23	.84
Discontinuation of antifungal treatment due to drug-related toxicity	10	19.2	5	10.0	−0.11	-	-	−0.30	0.08	.26
Probable invasive fungal disease	5	9.6	0	0.0	−0.08	-	-	−0.38	0.23	.06

Note: A positive value indicated favourable results for the intravenous itraconazole group. Non-inferiority of intravenous itraconazole compared with liposomal amphotericin B was concluded if the lower limit of the 90% confidence interval was larger than −0.1.

[a]Adjusted for risk (high or low), prophylactic antifungal treatment (yes or no), sex and age (age at enrolment < 60 y or ≥60 y).

[b]There were no cases with baseline infections.

[c]Could not be calculated because all the patients survived.

TABLE 3 Adverse events

	Liposomal Amphotericin B Group (n = 52)				Intravenous Itraconazole Group (n = 50)			
	Grade 3		Grade 4		Grade 3		Grade 4	
	N	%	N	%	N	%	N	%
Elevated alkaline phosphatase	1	1.92	0	0.00	1	2.00	0	0.00
Elevated alanine transaminase	4	7.69	0	0.00	0	0.00	1	2.00
Elevated aspartate transaminase	1	1.92	0	0.00	2	4.00	0	0.00
Increase in total bilirubin	2	3.85	0	0.00	1	2.00	1	2.00
Elevated creatinine levels	2	3.85	0	0.00	1	2.00	0	0.00
Elevated γ-glutamyltransferase levels	5	9.62	0	0.00	2	4.00	0	0.00
Hypomagnesemia	1	1.92	0	0.00	0	0.00	0	0.00
Hypokalaemia	18	34.62	11	21.15	9	18.00	5	10.00
Hyponatremia	0	0.00	0	0.00	0	0.00	1	2.00
Chills	1	1.92	0	0.00	0	0.00	0	0.00
Nausea	4	7.69	0	0.00	2	4.00	0	0.00
Headache	2	3.85	0	0.00	0	0.00	0	0.00
Dyspnoea	2	3.85	0	0.00	5	10.00	0	0.00
Hypoxia	2	3.85	0	0.00	6	12.00	0	0.00
Allergic reactions/hypersensitivity	0	0.00	1	1.92	0	0.00	0	0.00
Hypotension	0	0.00	0	0.00	0	0.00	2	4.00

Note: Grade 3-4 adverse effects, including ventricular arrhythmia, hot flashes, vomiting, cardiac ischaemia/infarction, cardiopulmonary arrest and hypertension did not occur in either group.

ineffectiveness of therapy in two cases and AEs excluding hypokalaemia in two cases. Grade 4 hypokalaemia subsequently occurred in three patients switched to LAmB. Therefore, these three patients were counted as grade 4 hypokalaemia in the ivITCZ group. Many of the patients with grade 3-4 hypokalaemia required potassium supplementation. Further, since oral potassium supplementation was

inadequate because of the extremely low levels of potassium, intravenous potassium drips were necessary. Hypokalaemia is a common complication of LAmB therapy, which sometimes triggers severe arrhythmia in patients with diarrhoea. It is one of the most fatal transplant complications in acute graft vs host disease (GVHD) patients, many of whom experience severe diarrhoea. Therefore, avoidance of hypokalaemia is very important in the management of haematological malignancies, including during hematopoietic transplantation.

A meta-analysis of randomised controlled trials by Chen et al[17] reported that ITCZ has a significantly better initial treatment response rate (RR) compared to amphotericin B deoxycholate (RR = 1.33, 95% CI: 1.10-1.61). In terms of its in vitro antifungal spectrum, amphotericin B shows a broader spectrum of activity than itraconazole; Boogaerts and colleagues reported that both intravenous and oral solutions of ITCZ are as effective and safer than amphotericin B deoxycholate as empirical antifungal therapy in cancer patients with febrile neutropaenia.[13] In addition, since the oral solution formulation resulted in a higher blood concentration than the capsule formulation, 65 persons were changed from an injection to an oral solution. In our study, since the ITCZ blood concentration of cases was not measured, only the intravenous formulation was used without switching to the oral solution.

In the LAmB group in our study, there were two cases of breakthrough infection and five cases of probable invasive fungal disease, whereas in the itraconazole group, neither breakthrough infection nor probable invasive fungal disease occurred. Further, there was no significant difference between groups in terms of probable invasive fungal disease or breakthrough infection. Although the small sample size is a study limitation, it is noteworthy that there was no case proven to be highly likely to be invasive mycosis in the ivITCZ group.

Some reports have described resistance to LAmB,[18] caspofungin[4] and micafungin,[8,12,19] which are classified as echinocandins, and itraconazole[14] and voriconazole,[5-7] which are classified as azoles. Increasing the frequency of use of one type of antifungal agent might increase the resistance to various fungi. Increased breakthrough infections due to resistance might lead to fatal outcomes. The use of different types of antifungals that are nearly as effective as empirical treatments might, on the other hand, reduce fungal resistance.

Although the differences between the groups were not significant in this study, the treatment discontinuation rate and AE frequency due to drug-related toxicity were lower in the ivITCZ group than in the LAmB group, indicating its safety impact. Further, the toxicity of ivITCZ was at least not greater than that of LAmB. Hence, although we were unable to prove the non-inferiority of ivITCZ as compared to LAmB, given that LAmB is more expensive than ivITCZ, our results suggest that it might be worth considering using ivITCZ as an alternative antifungal agent in the empirical treatment of patients with haematological malignancies with persistent fever and neutropaenia.

ACKNOWLEDGEMENTS

The authors would like to thank Dr Yasunobu Abe (National Hospital Organization Kyushu Cancer Center) for recruiting patients for this trial. The authors are grateful to all the patients, families, nurses and physicians who participated in this study. The authors would also like to show their appreciation to the independent monitoring committee members, Drs. Kazuo Tamura (Fukuoka University hospital), Yoshinobu Maeda (Okayama University hospital) and Koji Izutsu (National Cancer Center hospital). This study was supported by a Grant-in-Aid for Clinical Research from the National Hospital Organization.

CONFLICT OF INTEREST

IY reports personal fees from Celgene, Mundipharma, Bristol-Myers Squib, Shire Japan, Janssen Pharmaceuticals, Mochida Pharmaceutical Co., Ltd., MSD KK, Takeda Pharmaceutical Co. Ltd. and Taiho Pharmaceutical, and grants and personal fees from Kyowa Hakko Kirin Co. and Chugai Pharmaceutical Co. that were not related to the submitted work. MH reports grants from Chugai Pharmaceutical Co. that were not related to the submitted work. YM reports personal fees from Janssen Pharmaceuticals that were not related to the submitted work. CY reports personal fees from Sumitomo Dainippon Pharma Co., Ltd., and Janssen Pharmaceutical KK that were not related to the submitted work. KS reports grants from the National Hospital Organization during the conduct of the study, grants from Novartis, GlaxoSmithKline, Janssen Pharmaceutical, AbbVie Inc, Sanofi, MSD KK, Alexion Pharmaceuticals and Daiichi Sankyo, and grants and personal fees from Takeda Pharmaceutical, Bristol-Myers Squibb, Ono pharmaceutical and Celgene that were not related to the submitted work. SY reports grants from Kyowa Kirin Co., and Chugai Pharmaceutical, and personal fees from MSD KK that were not related to the submitted work. YK reports grants from the Research Program on Emerging and Re-emerging Infectious Diseases from the Japan Agency for Medical Research and Development (AMED), Grant-in-Aid for Scientific Research (C) from the Japan Society for the Promotion of Science and Pfizer Academic Contributions, as well as personal fees from MSD KK, Meiji Seika Pharma Co. Ltd., Pfizer Japan Inc, Astellas Pharma Inc and Biofermin Pharmaceutical Co. Ltd. that were not related to the submitted work. HN reports grants and personal fees from Janssen Pharmaceutical KK, Celgene Corporation, Mundipharma KK, Bayer Yakuhin Ltd., Takeda Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Eisai Co., Ltd., Bristol-Myers Squibb, Ono Pharmaceutical Co., Ltd., Gilead Sciences, Inc, Zenyaku Kogyo Co., Ltd., AstraZeneca PLC and SymBio Pharmaceuticals Ltd., grants from AbbVie GK, Solasia Pharma KK, HUYA Bioscience International, Otsuka Pharmaceutical Co., Ltd. and IQVIA Services Japan KK, and personal fees from Roche Ltd. and Sanofi KK that were not associated with the submitted work. The other authors have nothing to disclose.

AUTHOR CONTRIBUTIONS

IY involved in the conception, design and funding acquisition. IY and AMS involved in the protocol writing. ST performed the statistical analysis design. IY, IC, MH, YM, YI, SY, TK, HI, HN, TK, CY, FT, HY, KT, HU, TS, TS, YN, CY, SK, KS, SY, AS and HN involved in the provision of study materials or patients. IY, AMS, IC, MH, YM, YI, SY, TK, HI, HN, TK, CY, FT, HY, KT, HU, TS, TS, YN, CY, SK, KS, SY, AS and HN involved in the provision or collection of data. IY, AMS and ST performed the

data analysis and interpretation. YK and YM involved in the evaluation of fungi. IY, AMS and ST involved in the manuscript writing. All authors performed the final approval of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Yoshida I, Saito AM, Tanaka S, et al. Intravenous itraconazole compared with liposomal amphotericin B as empirical antifungal therapy in patients with neutropaenia and persistent fever. *Mycoses*. 2020;63:794–801. https://doi.org/10.1111/myc.13100